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Asthma induced by enkephalin

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Summary and conclusions

A total of 291 diabetics were studied to see whether an asthmatic reaction was associated with facial flushing induced by chlorpropamide and alcohol. Of these patients, 191 reported facial flushing, of whom 12 reported breathlessness as well. Of these 12, five also described wheezing, and respiratory function tests showed them to have asthma. Three of these five patients underwent further tests, which showed that the asthmatic reaction could be prevented by giving disodium cromoglycate and the specific opiate antagonist naloxone. One patient developed wheezing when given an enkephalin analogue with opiate-like activity.

Asthma induced by chlorpropamide and alcohol was concluded to be mediated by endogenous peptides with opiate-like activity such as enkephalin.

Introduction

Facial flushing after alcohol is well recognised in diabetics receiving chlorpropamide. Occasionally patients report breathlessness and even wheezing during chlorpropamide-alcohol flushing (CPAF).¹ We investigated the incidence and nature of this reaction and have shown that CPAF is caused by increased sensitivity to endogenous opiates such as enkephalin, a pentapeptide with opiate-like activity.^{2,3} We therefore carried out a study to determine whether enkephalin was the cause of wheezing in these patients. We attempted to block the wheezing with the specific opiate antagonist naloxone and to induce it by infusing the enkephalin analogue (*H*-Tyr-D-Ala-Gly-McPhe-Met (O)-ol)-enkephalin (DAMME, Sandoz).

Patients and methods

We asked 291 diabetics taking chlorpropamide to describe any symptoms after drinking 40 ml sherry in one minute. Any patients who described wheezing and CPAF during this test were then asked to perform a series of alcohol challenge tests. The tests, which were performed on separate days after bronchodilator treatment had been stopped for at least 12 hours, were as follows: (1) 12 hours after

taking 250 mg chlorpropamide patients drank 100 ml sherry over five minutes; (2) 20 minutes before drinking sherry as above patients inhaled 20 mg disodium cromoglycate; (3) 12 hours after taking 250 mg chlorpropamide patients drank 40 ml 95% ethanol diluted in 60 ml water (about equivalent to the sherry's ethanol concentration) over five minutes; (4) 12 hours after taking 250 mg chlorpropamide patients inhaled 5 ml 10% ethanol in physiological saline; and (5) 12 hours after taking 5 mg glipizide patients drank 100 ml sherry over five minutes.

Three baseline measurements of forced expiratory volume in one second (FEV₁) and slow vital capacity (VC) were made with a Vitalograph before the challenge tests and then at five-minute intervals for 15 minutes and at 15-minute intervals for 75 minutes after the alcohol had been administered. Blood samples were taken in test 1 via an indwelling venous cannula 10 minutes before and at 0, 5, 10, 20, 30, and 60 minutes after the patient had finished the sherry to determine total IgE concentration, absolute eosinophil count, and serotonin concentration. IgE concentration was measured by solid-phase radioimmunoassay and serotonin assayed on whole blood fluorometrically.⁴

Naloxone block of asthma—Two patients (cases 1 and 2) received naloxone 0.4 mg min and on another occasion saline infused through an indwelling venous cannula. The infusion began five minutes before test 1 and continued for 20 minutes thereafter.

Infusion of enkephalin analogue—Two patients who exhibited CPAF (one who reported concomitant wheezing (case 1) and one who did not (case 4)) were given an intravenous infusion of 0.25 mg of the enkephalin analogue DAMME over two minutes. They had taken no chlorpropamide for two months and no other drugs for 48 hours before the infusion. Measurements of FEV₁ and slow VC were made with a Vitalograph.

Results

Of the 291 diabetics studied, 191 reported facial flushing after chlorpropamide and alcohol. Twelve patients described breathlessness accompanying the CPAF, of whom five also wheezed; respiratory function tests showed these five patients to have asthma. Two patients known to have asthma and who showed CPAF, however, did not report any respiratory symptoms during the flush and their FEV₁ did not change after challenge with chlorpropamide and alcohol.

Of the five patients who described wheezing during CPAF, three agreed to undergo the series of alcohol challenge tests. Their case histories are given below.

Case 1—This 55-year-old man had experienced mild productive cough during the previous winter but denied any wheezing or history of asthma. There was no family history of atopy or asthma. He did not smoke. Clinical examination, chest radiography, and blood count showed no abnormalities. Skin-prick tests with various common allergens gave negative result. Results of pulmonary function tests were: FEV₁ increased from 2.0 l to 2.2 l after two puffs of salbutamol (predicted value 2.4 l); VC increased from 2.7 l to 2.9 l after salbutamol (predicted value 3.0 l); and carbon monoxide pulmonary diffusing capacity (D_lco) (single breath) was 8 mmol/min/kPa (24 ml/min/

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mm Hg) (predicted value 6.8 mmol min kPa; 20 ml min mm Hg).

Case 2—This 54-year-old man was known to have asthma, wheezing first being noted when he was aged 25. There was no family history of atopy or asthma. He used a salbutamol inhaler regularly and did not smoke. Clinical examination, chest radiography, and blood count showed no abnormalities. Prick tests gave positive results for allergens to cat, dog, dust, and house-dust mite. The results of pulmonary function tests were: FEV₁ increased from 1.5 l to 1.8 l after salbutamol (predicted value 3.1 l); VC increased from 2.8 l to 3.1 l after salbutamol (predicted value 4.1 l); and D₁co was 11.4 mmol min kPa (34 ml min mm Hg) (predicted value 9.1 mmol min kPa; 27 ml min mm Hg).

Case 3—A 46-year-old man had developed asthma in childhood and had seasonal hayfever. His wheezing was always mild and required no treatment. He did not smoke, and there was no family history of atopy. Clinical examination, chest radiography, and blood count showed no abnormalities. Prick tests gave positive results to grass and tree pollens and allergens to house dust, house-dust mite, and mixed mould. The results of pulmonary function tests were: FEV₁ increased from 3.8 l to 4.2 l after salbutamol (predicted value 4.0 l); VC increased from 5.4 l to 6.1 l after salbutamol (predicted value 5.1 l); and D₁co was 15.4 mmol min kPa (46 ml min mm Hg) (predicted value 11.4 mmol min kPa; 34 ml min mm Hg).

Figure 1 shows the results of alcohol challenge tests in these three patients. FEV₁ fell substantially on challenge with sherry and chlorpropamide in each case (by 55%, 50%, and 21% respectively).

FIG 1—Responses of FEV₁ in three diabetics to challenge tests with chlorpropamide and sherry (—); chlorpropamide and sherry after disodium cromoglycate inhalation (---); chlorpropamide and ethanol (·····); and glipizide and sherry (- · - · -).

This fall was rapid and reversible. Administration of disodium cromoglycate blocked this response but did not prevent CPAF. Ethanol when taken by mouth after chlorpropamide, but not when inhaled, also induced CPAF and a fall in FEV₁. When glipizide was substituted for chlorpropamide no flush or change in FEV₁ was observed on challenge with sherry.

Total IgE concentrations, absolute eosinophil counts, and serotonin concentrations were normal and did not change in any of the patients.

NALOXONE BLOCK OF ASTHMA

Both patients tested (cases 1 and 2) reported an attenuation of respiratory symptoms when a naloxone infusion was given with chlorpropamide and sherry, and neither complained of wheezing. FEV₁ fell at five minutes in both patients but returned rapidly to near-normal during the infusion. In case 1 the maximal fall in FEV₁ with naloxone was only 22% compared with 55% without (fig 2). In case 2 FEV₁ had fallen at five minutes during naloxone infusion but at 15 minutes the fall was only 27% compared with 55% without naloxone; this difference persisted up to 60 minutes after the challenge.

FIG 2—Response of FEV₁ to chlorpropamide and sherry alone (—) and with naloxone infusion (---) in case 1.

DAMME INFUSION

One of the two patients given an infusion of DAMME (case 1) developed an asthmatic reaction after the infusion. His FEV₁ had dropped by 33% five minutes after the infusion, gradually returning to normal by 60 minutes (fig 3). He reported facial flushing, tightness of the chest, breathlessness, and wheezing. The other patient (case 4) was known to suffer from asthma but did not wheeze during the tests. She showed no change in FEV₁ after DAMME infusion despite intense facial flushing.

FIG 3—Fall in FEV₁ induced in case 1 by infusing the enkephalin analogue DAMME.

Discussion

These results show that chlorpropamide and alcohol can induce asthma, but unlike facial flushing wheezing is a rare feature of this interaction. Both responses are specifically due to

the action of chlorpropamide with alcohol; alcohol with other sulphonylureas produces no such effects.

We have shown that CPAF is caused by opiate peptides such as enkephalin,² and we questioned whether these peptides also mediated the asthmatic reaction associated with CPAF. We found that asthma induced by chlorpropamide and alcohol was partially blocked in two patients by the specific opiate antagonist naloxone. One of these patients developed wheezing after an infusion of the enkephalin analogue DAMME. Thus asthma induced by chlorpropamide and alcohol is mediated by opiate peptides such as enkephalin.

Ethanol alone has not been reported to cause asthma. Some drinks containing ethanol induce wheezing in asthmatic patients, but this is caused by congeners since ethanol has no effect.³ The asthma induced by congeners is, however, similar to that induced by chlorpropamide and alcohol in several respects: there is a rapid fall in FEV₁ on challenge with the drink, which persists for about one hour; none of our patients described further wheezing up to 12 hours after challenge; and total IgE concentration and total eosinophil count did not change. Hence neither type of asthma is likely to be mediated by specific reaginic antibodies, though they may both be prevented by administering disodium cromoglycate.

CPAF, and by implication enkephalin, may act as a triggering factor in some asthmatic patients, though not every such patient who shows CPAF wheezes during the reaction. In a patient who showed CPAF (case 4) FEV₁ did not change after DAMME infusion or on challenge with chlorpropamide and alcohol. Several other non-immunological triggers cause asthma such as hyperventilation, cold air, exercise, emotional stress, and some chemical irritants, but the mechanism is uncertain. Some of these triggers may activate neural pathways, either by autonomic reflex or by stimulation of the central nervous system. Even allergen-induced asthma may be partially mediated by an autonomic reflex, since it is blocked in animals by vagotomy⁶ and atropine⁷ and in man by atropine.⁸ These observations have led to the suggestion that acute bronchoconstriction is largely caused by reflexes in lung receptors mediated by pulmonary afferent and bronchoconstrictor efferent pathways in the vagus nerve.

Many autonomic nerve fibres are neither cholinergic nor adrenergic but peptidergic. These fibres are rich in peptides

such as enkephalin that probably act as neurotransmitters.⁹ Asthma induced by chlorpropamide and alcohol might be mediated by a neurotransmitter effect of these peptides; alternatively such peptides might act locally as hormones—for example, carcinoid tumours produce similar peptides and can induce asthma and facial flushing.

We have described a new cause of asthma—that is, the interaction of chlorpropamide and alcohol. We believe that this asthma is mediated by peptides with opiate-like activity such as enkephalin. Although this type of asthma is rare, other factors causing release of enkephalins may have the same effect in patients susceptible to asthma.

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SHORT REPORTS

Follow-up study of rubella vaccination in general practice

An article¹ on the vaccination of rubella-susceptible women reported that out of 38 patients vaccinated only 25 appeared to have responded satisfactorily. As a result of this apparently low seroconversion rate further investigations were carried out. The feasibility of offering vaccination to rubella-susceptible women attending a contraceptive clinic has been stated.²

Method and results

Patients were asked by questionnaire about the brand of vaccine used, how long it had been in their possession, and whether kept in a refrigerator, handbag, or elsewhere. No difference in results was shown, but all had been supplied with Cendevax (Cendehill, Smith Kline & French). The 38 vaccinated patients had been bled to check the results of vaccination. All those with HAI titre of $\geq 1/80$ were considered to have an unsatisfactory response and those with some, but inadequate, immunity on first testing ($\leq 1/30$) that did not increase to $\geq 1/30$ after first vaccination were also considered unsatisfactory. Thirteen patients (19%) were considered to have an unsatisfactory response and it was decided to revaccinate them with RA27/3HT (a high-titre vaccine kindly made available to us by the Public Health Laboratory). The delay between the initial vaccination and re-vaccination of non-responders was between 30 and 42 weeks. A further sample of blood was therefore taken to check the initial findings and also

to see if the passage of time had raised the titre. Eight patients now had adequate titres—that is, ranging from 1/160 to 1/1280. Out of the five remaining patients, one still had no response but developed a titre of 1/320 after having RA27/3HT, and one had become pregnant and could not be revaccinated although her titre had risen only marginally from 1/20 to 1/40. All the remaining three had some immunity to start with, but inadequate by our advised criteria. Further time had made no difference to these and vaccinating with RA27/3HT only slightly raised the titres to 1/30, 1/40, and 1/80, respectively.

Comment

Thirty-eight patients with little or no immunity resulted in 13 inadequate responses to vaccination initially. Three of these were in patients with some antibodies, but at a low level, and their titres rose by very little after revaccination. Possibly this means that an antibody titre of 1/30 may in fact indicate adequate immunity against rubella as well as from the attenuated rubella in the vaccine. Of the other ten, only one definitely required vaccination. The response with the Cendehill strain is known to be slower than with RA 27/3 (Almevax B/W),³⁻⁵ so it should not be surprising that out of 13 original poor responders eight should subsequently have had adequate titres after more than six months. Possibly this indicates that the speedier response with Almevax might be more appropriate for general use.

Apparently very little benefit has been derived from checking immunity levels after vaccination. Only one patient out of 38 appears to have benefited. In terms of work load to the doctor, inconvenience